CHEMICAL & ENGINEERING NEWS

C&EN

JANUARY 31, 1994

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CUSTOM CHEMICALS

New supplier-customer relationships are changing the industry **Page 26**

CHEMICAL & ENGINEERING NEWS
C&EN
JANUARY 31, 1994

NEWS OF THE WEEK

■ Plutonium from dismantled nuclear weapons presents a clear danger, says a National Academy of Sciences panel that urges immediate attention to prevent risks. **Page 6**

■ Fourth-quarter 1993 chemical earnings show dramatic increases over year-earlier figures, continuing a trend that includes no overall improvement in sales. **Page 7**

■ German chemists develop a simple, inexpensive method for making dihydroxyacetone phosphate, and reacting it at once with aldehydes to make unusual sugar derivatives. **Page 8**

■ NIH forum will help agency draft guidelines for academic research sponsored by industry and government—encouraging technology transfer while protecting taxpayers' investment. **Page 8**

■ Russian chemist is jailed after refusing to attend trial on charges of revealing chemical weapons information. **Page 9**

■ EPA announces plans to fund more than 70 projects under Administration's Environmental Technology Initiative, including program with industry to develop new hazardous waste cleanup technology. **Page 9**

COVER: Worker charges reactor for custom project at Salsbury Chemicals, Charles City, Iowa

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BUSINESS

Use of acrylic resins is forecast to increase steadily through 1997, bolstered by recovering U.S. economy and the compounds' wide range of markets and end uses. **Page 13**

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EPA's list of toxic chemicals that could be accidentally released enables communities to plan for risk management, but it shows little coordination with OSHA's list of hazards. **Page 16**

President's blue-ribbon advisory panel on sustainable development met in Seattle to learn from Northwest Pacific citizens who have been pursuing innovative strategies. **Page 17**

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Research links man-made mimics of estrogen to reproductive abnormalities and cancer in humans and wildlife; evidence on risks to humans is fragmentary but suggestive and worrisome. **Page 19**

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NSF has awarded 14 planning grants to groups developing proposals to reform undergraduate chemistry curricula. **Page 25**

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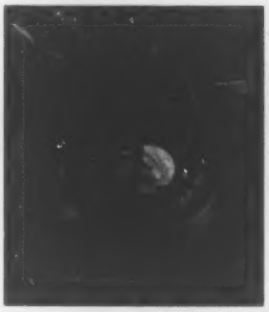

The custom chemicals industry, which serves drug, agrochemical, and other companies, is confronting new market forces that are pushing more suppliers and customers into long-term relationships. Page 26

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LETTERS

Chemists have become watchers

Why starting salaries of B.S. chemical engineers are 40% higher than those of chemists, the question addressed by Ted Logan (C&EN, Jan. 10, page 3), recalled the aphorism that goes: There are three kinds of people—those who make things happen, those who watch things happen, and those who don't know that anything is happening.

The earmark of the engineer is design. Thus, the culture of the engineer falls in the first category. It's been said that culture derives from the ancient guilds, artisans who made things.

Not so long ago the earmark of the chemist was synthesis. That culture, too, is in the first category. But the paradigm has been shifting, some say from alchemist to a sort of priesthood searching for a Holy Grail called scientific truth.

That paradigm shift plus the growing fascination with analysis and mathematical modeling has relegated chemists to the second category, that of watchers. Campus chemistry has become a spectator sport, more concerned with what is than with what can be.

In part that shift is due to the ease with which analytical data can be generated and published, especially when each announcement is trumpeted as a threat to the public's health. In part it's due to academic emphasis on problems that offer neat solutions. But today those are the trivial ones, divorced from what the public sees as important enough to pay for directly. So, enter the government that's there to help you. Its funneling of money into universities without benefit of free-market testing has corrupted the world view of chemistry faculty and their students.

Once, academic chemists made and taught the theory that their students were willing to pay to learn and that they made things for public use, as opposed to agency use. In both cases, they quickly learned the discipline of the marketplace. That refining process has been lost as chemistry faculty members have been more and more influenced by political and emotional forces.

Solution? Let's shift our educational focus from finding and introducing tools for which we hope to find (or never find) uses, to supplying tools to make good things happen. To do that we have to decide, first, what we want B.S. chemists to do. Here's my short list: materials behavior, that is designing (that engineer's word) structure for function; marketing in all its fascinating aspects from market research to packaging to global sourcing and sales; chemistry-based law from regulatory to intellectual property management; and biological chemistry from toxicology and epidemiology to prosthesis and dose-delivery design.

I can hear the shrieks from campus already: "But that's not chemistry!" To which my response is, "If chemical professionals don't prepare people for these tasks, who will?" Twenty-five years ago I wrote, "We are teaching students to play checkers with virtuosity when society wants them to play chess." We're still doing that except now it's world-class chess they want us to play.

Benjamin J. Luberoff
Summit, N.J.

Supporting minority scientists

I read with displeasure the letter by Kip Kimbrough titled "Why train more scientists?" (C&EN, Dec. 13, 1993, page 5). The writer appears to have misconstrued the National Science Foundation's reason for spearheading a drive aimed at producing more minority science graduates by the year 2000.

The number of minority science graduates in this country is at an all-time low. If the job market is flooded with scientists, minority scientists are certainly not the cause.

Kimbrough's letter further seems to suggest that chemistry programs should be shut down or that the graduation rate of chemists ought to be attenuated in order for employed chemists to retain their jobs. These, in my opinion are incongruous.

I find the NSF goal to be quite reputable. The idea is esteemed by many except for a few like Kimbrough who fail to apprehend the need for minority presence in all facets of science and technology.

Despite downsizing, layoffs, and belt-tightening by chemical and pharmaceutical companies, all of my colleagues who completed their degrees over the past six months are employed and delighted with their jobs. Some had four job offers.

We need to motivate people from mi-

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Steady Growth for Acrylic Resins Consumption Projected Through 1997

■ ***Projected upsurge in U.S. economy will spur growth in acrylic resins use of 5% per year between 1992 and 1997***

As the U.S. economy continues to recover, use of acrylic resins will rise from almost 2.2 billion lb in 1992 to 2.7 billion lb in 1997, according to a new study from industry consultant firm Freedonia Group. The study, "Acrylic Resins to 1997," projects that U.S. acrylic resin consumption will increase almost 5% annually during that period, up from 3% per year for the previous five years.

Improvements in the economy will stimulate consumption of acrylic resins in a host of markets and end uses including plastics modifiers, construction materials, adhesives, and paints and coatings, says William Baumgartner, an analyst with Freedonia. However, Baumgartner's new 157-page report notes use of acrylic resins will also rise because they allow manufacturers to formulate more "environmentally friendly" products.

Because acrylic resins may be suspended in water, they are ideal substitutes for traditional solventborne alkyds that are used, for instance, to formulate paints and coatings. As the more traditional solventborne alkyd paints and coatings dry, they release volatile organic compounds, contributors to the formation of atmospheric smog.

Government regulatory pressure has forced paints and coatings formulators to severely cut down on the use of solvents. In many cases, formulators have moved to alternative technologies—among them waterborne acrylics—in order to reduce solvent content in paints and coatings to the absolute minimum. Only some small paint segments have until now resisted the change to waterborne acrylics. Other opportunities do exist for acrylics to replace some solvents, such as in adhesives.

Baumgartner's study divides acrylic resins into two broad categories: acrylates, which accounted for 46% (or 1 billion lb) of acrylics consumption in 1992; and methacrylates, which accounted for the other 54% (or 1.2 billion lb) of acrylics consumption. Of the two classifications, Baumgartner projects that use of methacrylates will grow nearly 5% per year through 1997 and use of acrylates will grow at just over 4% per year.

As the construction market improves in the economic recovery that most economists are predicting for the next few years, demand for use of methacrylates in products such as glazing, building panels, lighting components, and plumbing parts will expand rapidly. Similarly, spiraling growth in the industrial/commercial category will raise methacrylate use in such products as industrial safety shields and signs.

A growing market for acrylates as polyolefin property modifiers and as a comonomer in specialty ethylene polymers will broaden use of acrylates in plastics production, says Baumgartner. Markets are also growing for acrylates in the manufacture of acrylic pressure-sensitive adhesives, especially for packaging applications, he adds.

In a breakdown of demand for acrylics by market and end use, the Freedonia study projects that industrial/commercial use of acrylic sheet for industrial safety barriers and signs will grow 8% annually between 1992 and 1997 to 175 million lb—faster than any other major market. In his study, Baumgartner points out that consumption of acrylic resins in the industrial/commercial segment actually declined 4% between 1987 and 1992.

The study does not discuss reasons for the earlier decline in this segment. But industry sources cite the slow economy and competitive pressure from polycarbonate for the decline. However, the study suggests that improvements in acrylic demand in the industrial/commercial category between 1992 and 1997 will be largely the result of a pickup in industrial equipment orders and a concomitant increase in demand for the safety barriers and face shields required by the Occupational Safety & Health Administration.

Rohm and Haas, ICI, and Cyro Industries, the three dominant vertically integrated producers of methyl methacrylate and acrylic sheet, could benefit if Baumgartner's predictions for the industrial/commercial segment growth materialize. Other markets that employ acrylic sheet and that may grow at or above the 5% annual average for all acrylic resins between 1992 and 1997 are construction materials (up 5%) and transportation (up

Industrial, consumer markets to pace U.S. acrylic resins growth

Millions of lb	1992	1997	% annual change 1992–97
Paints & coatings	669	795	4%
Construction	303	387	5
Textiles & fibers	233	288	4
Plastics modifiers	184	240	6
Adhesives & sealants	157	198	5
Transportation	123	165	6
Industrial/commercial	119	175	8
Paper binders	90	110	4
Consumer	48	70	8
Other markets[a]	229	267	3
TOTAL ACRYLIC RESINS	2,155	2,695	5%

[a] Includes printing inks, furniture polishes, water treatment polymers, and polymer concretes. **Source:** Freedonia Group

6%), including aircraft windows and boat shields. The growth rates are particularly significant for the potential profitability of ICI's July 1993 acquisition of three DuPont methyl methacrylate and acrylic sheet plants.

Growing demand for appliances, medical devices, data storage media, eye wear, and even dental fillings will push acrylic resin consumption up almost 8% per year to 70 million lb by 1997 in the consumer category, notes Baumgartner. Growth in the category, however, is from a rather small base of 48 million lb in 1992 compared with the 669 million lb Baumgartner says the paints and coatings market consumed in 1992.

The nearly 4% annual growth in consumption that Baumgartner predicts for paints and coatings is lower than the average 5% annual growth for all acrylic resins between 1992 and 1997. But the absolute increase of 126 million lb for paints and coatings is certainly much greater than the 22 million lb growth in the consumer category over the same period. So although growth in acrylic resins consumption in paints and coatings may appear to be below average, continued demand for waterborne and environmentally safer paints will mean that paints and coatings will continue to claim almost one third of acrylic resins consumption.

Other markets for which the study forecasts growth rates lower than the 5% average for all acrylic resins are paper (up 4% to 110 million lb), textiles and fibers (up 4% to 288 million lb), and the mixed bag of smaller "other markets" (up 3% annually between 1992 and 1997 to 267 million lb).

Mature markets for acrylic resins in printing inks, furniture polish, and polymer concretes will account for the below average growth in the study's other markets category. Use of acrylic resins as paper binders is also a fairly mature end use. It, too, will grow more slowly than the overall market for acrylic resins.

Acrylic resins used to produce acrylic fibers, chiefly for textile use, are a different matter. Acrylic fiber production has been on the downswing for a number of years. DuPont, for instance, shut down its 200 million-lb-per-year acrylic fiber capacity in 1990, leaving only Monsanto and Cytec as principal producers.

The study projects that acrylic fiber will continue to lose market share to other fibers such as cotton in the production of active wear and fleece, and wool in the production of sweaters. Other textile uses for acrylic resins are mostly slow-growing mature markets. They include use of acrylic resins as backing for curtain and drapery fabrics, and as binder for insulating fiberfill.

Copies of the study, "Acrylic Resins to 1997," are available from Freedonia Group, 3570 Warrensville Center Rd., Suite 201, Cleveland, Ohio 44122-5226. The cost is $2,600.

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CUSTOM CHEMICALS

Move toward long-term supplier-customer relationships is changing industry's face

Stephen C. Stinson,
C&EN Northeast
News Bureau

Driven by needs to cut costs and raise operating efficiencies, drug companies worldwide are turning more than ever to custom chemical producers to supplement or replace their own manufacturing. This is an important trend, because drug companies have historically taken the biggest share of custom chemical production. The agrochemical industry, the second largest client of custom producers, is under many of the same pressures.

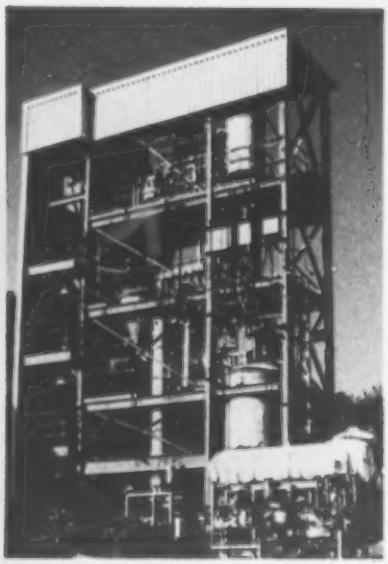
Yet at the same time, the fine chemicals industry, which furnishes custom production to the drug, agrochemical, and other specialty chemical industries, is in the midst of a profound metamorphosis. Wide-ranging shifts in ownership of fine chemical facilities are changing the landscape of custom production. In addition, the U.S. in particular is the focus of new custom production marketing campaigns by consortia of fine chemical firms in the U.K., Eastern Europe, and former Soviet republics.

Consultant Enrico T. Polastro of Arthur D. Little International in Brussels, outlines the pressures on the drug industry. First, he says, the patterns and philosophies of health care are changing. Second, governments are cracking down on costs of drugs and are openly hostile to the research-oriented drug firms. Third, regulatory agencies are raising the heights of hurdles regarding drug approval, production process specifications, environmental protection, and worker safety. Fourth, life cycles of products are growing shorter as delays in product approval and registration erode patent lives, and competitors are getting ever better at coming up with "me-too" products. And finally, the drug companies' own shareholders are growing more demanding and impatient. Many of these same pressures afflict the agrochemical, food additive, flavor and fragrance, and dyes segments of the fine chemicals industry, which are also customers for contract chemical production.

To Polastro, cutting costs and increasing efficiencies to meet these pressures lead logically to an examination of manufacturing. In particular, specialty chemical companies of all kinds should revise their manufacturing stances to the broader policy of "sourcing," he says. In a total sourcing policy, in-house manufacturing becomes only one option for procuring intermediates and active ingredients.

Among factors that mitigate against in-house fine chemical production, Polastro cites the disproportionate amount of capital that production capacity consumes. In addition, the true strategic functions of drug, agrochemical, and other specialty chemical companies are research, development, and marketing, he maintains, not manufacturing. Polastro also points to in-house manufacture—as it is now done—as riddled with pockets of inefficiency, leaving plenty of room for improvement. Increasing environmental hurdles also make in-house production a burden. And there is no logic to in-house production when so much custom chemical production capacity is available at outside firms.

Specialty chemical firms seem to be only too aware of these factors and are decreasing their reliance on in-house production and using more custom production. Between custom producers and their clients, there is an evolution toward what the custom producers call partnership, which is a long-term one-on-one relationship. Marc New, director of pharmaceutical fine chemicals for Lonza in Basel, Switzerland, traced this evolution in remarks to attendees at ChemSpec Europe '93 in Basel, Switzerland.



ChemDesign plant in Fitchburg, Mass., exemplifies advanced equipment and environmental safeguards needed at a modern custom production plant. Clockwise from above: Location of plant next to Leominster State Forest demands environmental concern; reactor from Swiss firm Buss enables safe hydrogenations; chiller uses liquid nitrogen to condense volatiles from air coming from all vessels; water treatment plant converts waste to inorganic salts for disposal; sales vice president William Scott indicates vent that goes from each vessel to the chiller.

New (pronounced Nef) notes that in the past there have been two opposing chemical marketing stances: one customer-many suppliers and one supplier-many customers. An example of one customer-many suppliers was Smith Kline & French's H2 antihistamine ulcer drug, cimetidine. When it first introduced the drug, Smith Kline marshaled an array of custom producers to make cimetidine. Everyone, including Lonza, seemed to be doing something for cimetidine—an intermediate or a reaction step.

But New suggests that such a situation might never recur. This is because of the increasing complexity of drug molecules and the desires of drug companies for rapid and secure production arrangements.

Complex molecules often require new chemical technologies that only a few firms can afford to perfect and maintain. Instruments for increasingly sophisticated analyses and specifications of quality are also costly. Security of supply means that custom producers must prove themselves able to comply with environmental regulations, including those for waste management. Drug companies cannot afford links to suppliers that may be shut down for environmental reasons. New thus sees an evolution toward partnerships as opposed to "buying." In buying, a customer qualifies several suppliers and stimulates competition on price. A partnership would be a close, thoroughgoing, long-term relationship between a drug company and one or two suppliers.

New's example of one supplier-many customers is Lonza itself. He cites the

company's 2-aminothiazole-4-acetic acid derivatives, which are attached as side chains to newer cephalosporin antibiotics of many drug firms. Though each thiazole side chain may be slightly different, they all come from Lonza's "tree" of such structurally related compounds.

New, however, sees an evolution away from this situation and toward partnerships. This is because drug companies are moving away from research to discover me-too compounds. Finding just one more cephalosporin or angiotensin-converting enzyme (ACE) inhibitor for high blood pressure is not as attractive as discovering an antiobesity or anti-Alzheimer's agent. The cost of R&D to discover and market a me-too drug is about the same as that for a new drug type. But the me-too drugs will enter a heavily competitive market in which the drug company is unlikely to recover the cost of R&D.

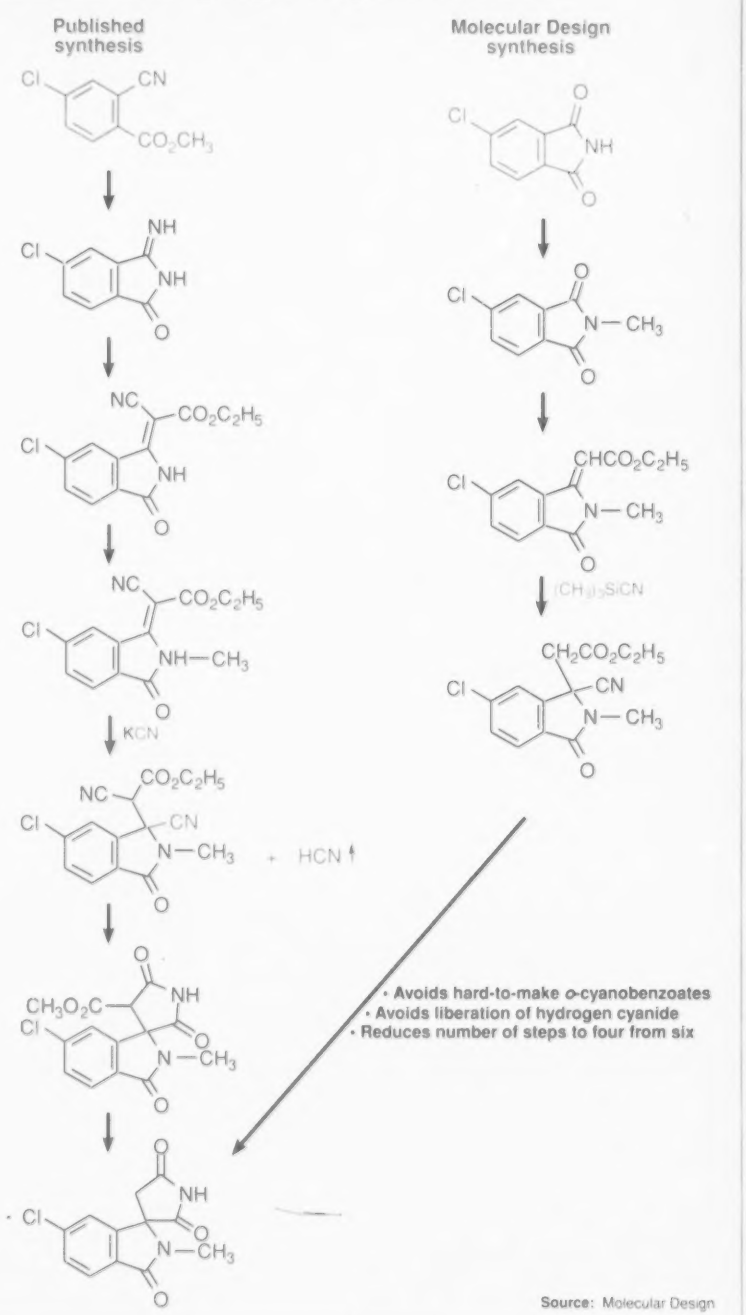
The only exception New sees to this trend away from the one supplier-many customers situation is in producing generic versions of drugs going off patent. This is because the generics industry is price-driven, and partnerships and customer loyalties are nonexistent. This situation leads to a shakeout among suppliers, leaving the one with the most environmentally friendly and cost-efficient process to supply many generic drug houses. New cites the Hoechst process for the anti-inflammatory agent ibuprofen as an example.

Supplying a $12.5 billion market

The dollar value of custom chemical production is hard to gauge. Client companies do not disclose much for fear of giving information to competitors. In addition, custom producers are bound by secrecy agreements. And analysts disagree on what and how much to count.

For example, some producers take a proprietary raw material from a client, perform one or a few synthetic reactions on it (tolling), and send the product back to the client. Should these producers claim the whole value of the product at that point as their "sales"? Or should they be limited to some estimated value of what they added themselves? And what of a standard intermediate in someone's catalog that has only one buyer one year? Is that intermediate now "custom-produced"? And does "manufacture" include physical processes as well as chemical reactions?

Databases can help improve synthetic schemes



Bearing all these caveats in mind, analyst Jean-Charles Pasquier of the consulting firm Eurekem Conseil in Courbevoie, France, puts the worldwide value of custom chemical production at $12.5 billion. About 600 producers employ 45,000 people, he says in his recent study of the subject. The U.S. and Europe account for 400 of these firms.

For his part, to show how estimates can vary, Polastro of A. D. Little puts the value of the entire world fine chemicals market at between $26 billion and as much as $34 billion. This represents only intermediate compounds or bulk active ingredients. It does not include costs of administration, sales, R&D, formulation, packaging, or profit, which all appear in the price of the finished product. Polastro's estimates are lower than those of many other analysts, and he ascribes this to the small proportion of the cost of fine chemicals in the prices of finished products.

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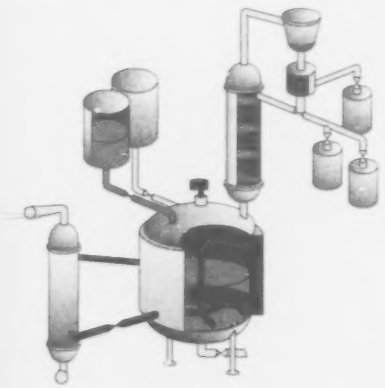

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He breaks down the value of fine chemicals production—custom, merchant, and captive—into $7 billion to $9 billion for the U.S., $12 to $15 billion for Europe, $6 billion to $7 billion for Japan, and $1 billion to $3 billion for the rest of the world. Polastro cites the U.S., Europe, and Japan, "the triad," as the fine chemicals leaders. He has argued that there may be a strong trend under way to transfer fine chemicals production from the triad to such places as China, India, and Southeast Asia.

Within fine chemicals worldwide, Polastro assigns $15 billion to $17 billion worth to the drug industry. Of that amount, 40% is produced by drug firms for their captive use, and 60% is sold by fine chemicals companies to drug firms on the merchant market. Of the merchant market, $2 billion to $3 billion worth is custom produced. Dollar sales of fine chemicals for drugs are growing 4 to 5% annually, Polastro says.

Pesticides account for $5 billion to $7 billion worth of fine chemicals, growing at 2 to 3% per year, the Brussels analyst estimates, 40% in the merchant market, and $300 million to $500 million custom-produced. The amount of fine chemicals that are custom-produced for such end uses as food additives, flavors and fragrances, and dyes is smaller than the amount for drugs and pesticides and is too hard to pin down exactly, Polastro says.

Food additives represent a $1.5 billion to $2 billion fine chemicals market, increasing 2 to 3% yearly, and 50% are merchant sales. Flavors and fragrances are also a $1.5 billion to $2 billion fine chemicals market, growing 2 to 3% per year, and 50% are merchant sales. Dyes use $1 billion to $2 billion worth of fine chemicals, annual growth rates are 1 to 2%, and 40% of that is merchant sales. The fine chemicals market trails off into a collection of miscellanies worth $2 billion to $3 billion, growing at 2 to 3% per year. Even the proportion of merchant versus captive sales is impossible to estimate in this portion of the market.

Eurekem Conseil's Pasquier notes a regional influence on attitudes toward buying and selling custom production services. On the issue of buying a compound or making it in house, he says, "If the U.S. groups are already in favor of the 'buy' attitude, it is not yet the case in Europe. Most European phar-

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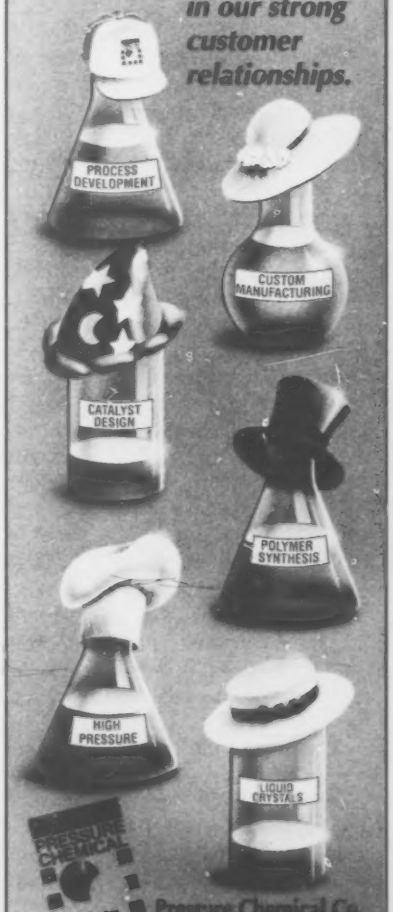

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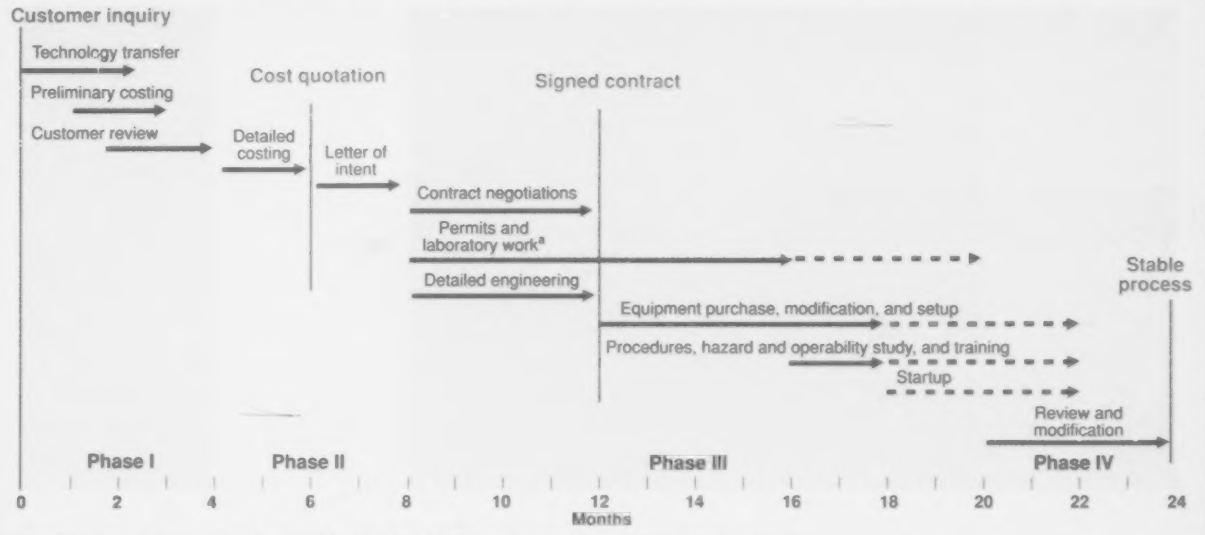
Though custom producers can respond in a week, production may not start for 18 months



a Regulatory permits may be speeded up because agencies are familiar with company performance. **Source:** Ruetgers-Nease

maceutical groups were always pharmaceutical companies. This is one of the reasons why [in-house] production is more frequent in Europe. There is, however, a gradual change in attitude, and the European market for contract manufacturing is expected to develop in the near future."

In noting other regional differences, Pasquier says that custom chemical production companies in the U.K. are active and well organized among trade associations, and well known throughout the world. The activity of these British companies shows up in their recently launched campaign, "North America Now," which aims at publicizing their expertise on the North American continent.

Of the two dozen or so French companies, he says that they "are less known abroad. The customer approaching these companies has the impression that the business is organized like a private club with high entry barriers for new members."

The Italian fine chemicals industry is very advanced, he says, but has evolved along a different direction. Weak protection for patents in Italy has led to an extensive industry to make standard intermediates and generic active ingredients, but only little activity in custom production. "As a result," Pasquier says, "Italy is not a very important country for contract manufacturing in Europe, in spite of the fact that its fine chemicals industry is much more developed than in [some] other European countries."

Ironically, Germany is also underrepresented in custom production. "When compared with the U.K. or France, one would expect to find about 60 companies in this business in Germany. In fact, only 12 companies have been identified.

"It is somewhat difficult to explain this situation," he says. "The general opinion is that the large German chemical groups have enough production facilities available to manufacture [the chemicals] themselves. This explanation, however, is not satisfactory, since if it is economically justified for other Western groups to subcontract production during the launching period of a new product, it should also be attractive for a German group.

"On the other hand, large chemical groups are present in neighboring Switzerland, and contract manufacturing activities are very developed there."

An industry in flux

Easily the most spectacular event in the ongoing reconfiguration of the custom synthesis industry has been the fragmentation of MTM's chemical empire. Headquartered in Yarm, England, MTM (which once stood for Marlborough Technical Management) spent the 1980s weaving together a fabric of chemical companies, several of which were American and several of which engaged in custom production. Falling on hard times, MTM began the 1990s by selling off these companies to pay down debt.

The first U.S. firm out of the MTM fold was Farchan Laboratories, Gainesville, Fla., in a management buyout led by president and original founder John Cochran. Farchan has specialized expertise and equipment to make acetylene and organosilane derivatives.

And Jack Dickstein, founder of both Dajac Laboratories and Monomer Polymer Corp., Southampton, Pa., was able to buy back Dajac from MTM in 1991 and Monomer Polymer in 1993. The reconstructed firm has been named Monomer Polymer & Dajac Laboratories, and Dickstein is moving the headquarters to Feasterville, Pa.

Other pieces of MTM were bought up by BTP (which once stood for British Tar Products), Manchester, England. Indeed, it was from BTP that Dickstein redeemed Monomer Polymer Corp. Other MTM units obtained by BTP include Lancaster Synthesis of Windham, N.H., and Morecamb, England; and Hardwicke Chemical Co., Elgin, S.C. BTP also got the now defunct Fairfield Chemical Co. from MTM, combined part of it with Lancaster Synthesis, and closed the Fairfield plant in Blythewood, S.C.

International Specialty Products (ISP), Wayne, N.J., purchased MTM's plant and fine chemicals business in Colum-

Directories help buyers choose among the hundreds of prospective sellers

People seeking contract chemical production can find providers of such services in several directories. For example, the Custom Synthesis & Custom Manufacture section of the American Chemical Society's "Chemcyclopedia" gives five- to 15-line listings of 165 firms with summaries of the capabilities of each. The current 1994 edition is available from ACS, Sales & Distribution Department, 1155—16th St., N.W., Washington, D.C. 20036, at a cost of $60.

Brandon Associates has published the 1994 edition of "The Brandon Guide to Custom Synthesis Services—North America," which sells for $190. The book gives one-page entries for 350 companies, cross-indexed by 200 chemical processes. The entries include equipment and processes available; details of pollution control, waste management, and analytical instrumentation; and whether the plant is approved by the Food & Drug Administration. Also available is the 1993 edition of a European guide to 300 companies for $225. Both books may be ordered from Brandon Associates, P.O. Box 1244, Merrimack, N.H. 03054.

Custom Guide Co. has published the latest, ninth, edition of "Custom Processing Services," which sells for $300. It gives one-page entries for almost 300 companies and is in loose-leaf format so users can make their own additions; the price includes future supplements. One index lists 25 unit operations and 130 chemical reactions and a second index lists plant locations. Users new to buying custom production can compile a list according to capabilities and then visit those companies that are closest. The directory may be ordered from Custom Guide, P.O. Box 358, Closter, N.J. 07624.

Quest Data's "A Guide to Custom Chemical Manufacturing & Processing" has multiple-page entries for each of 425 North American, European, and Japanese companies. In addition to equipment and processes available, a list of catalog chemicals produced is given. Entries include provisions for pollution control and waste disposal, analytical instruments available, and FDA approvals. The guide can be ordered for $135 from Quest, P.O. Box 210288, Nashville, Tenn. 37221. The price includes three updates at six-month intervals.

The Synthetic Organic Chemical Manufacturers Association has published its "1993/94 Commercial Guide," which lists its 125 member companies that do custom production. The capsule entries list contacts, equipment available, reaction capabilities, and details of analytical and waste disposal. The price of the guide is $25 and it is available from SOCMA, P.O. Box 79106, Baltimore, Md. 21279.

The directory chapter of Eurekem Conseil's "Contract Manufacturing in the Fine Chemical Industry" gives one-page entries for each of 350 U.S. and European firms. Included are lists of processes and equipment available; numbers of employees; FDA or ISO 9000 certifications; names of contacts; and telephone, telex, and fax numbers. The 640-page book also has a business overview chapter and one-page descriptions of 180 reactions used in contract manufacture. The study is available for $1,650 from S.E.T.E., 5 Rue Jules Lefebvre, 75009 Paris, France.

bus, Ohio, once known as Orsynex. ISP, in turn, is the recently founded, publicly owned company set up for the purpose of owning the chemicals business of privately held GAF Corp.

Besides the atomization of MTM, other significant events in the custom synthesis industry have included the divestitures of the chemical businesses of American Cyanamid, Eastman Kodak, Outokumpu (the Finnish metals and natural resources firm), and W. R. Grace.

Cyanamid set up its fine chemicals business as Cytec Industries, headquartered in West Paterson, N.J., and distributed shares in the new company to its own shareholders at the rate of one Cytec share for every seven Cyanamid shares held. Outokumpu sold its holdings in OM Group in a public offering. The Finnish company had assembled that metal salts producer company from Mooney Chemicals, Cleveland; Outokumpu Chemicals, Kokkola, Finland; and Vasset, Ezanville, France.

Managers of Grace's organics division bought their company and named it Hampshire Chemical Corp. Based in Lexington, Mass., Hampshire includes the former Grace organic and polymer divisions, Evans Chemetics, and Grace Rexolin of London, England.

Elsewhere in custom chemical production, Zeeland Chemicals, Zeeland, Mich., formerly owned by Hexcel, has become part of the Cambrex Corp. family of companies. Freedom Group has acquired Hilton Davis Co. of Cincinnati from PMC. In addition, Catalytica has bought a fine chemicals plant from Sandoz Agro in East Palo Alto, Calif. This is Catalytica's first producing facility, which it will use partly for custom production.

Sepracor is another company that has bought its first producing plant. The firm acquired Pharmaglobe, near Halifax, Nova Scotia. And United Chemical Technologies (UCT) has bought the specialty silanes and silicones business and plant in Bristol, Pa., from Hüls America. A coming change is the intended sale by Exxon of its Callaway Chemical Co., Columbus, Ga., a water treatment, paper, and textile chemical firm that also offers custom production.

Changes of ownership from MTM to BTP seem to have benefited the component firms involved. Vice president James Guy of Lancaster Synthesis in Windham, N.H., says his operation has stronger financial backing under BTP. For now, Lancaster has no plant in the U.S. but produces in Kirkby, England. The company does custom production on a scale of 500 g to 500 kg. Guy says that Lancaster may build a plant in the U.S. in 1995 or 1996.

Lancaster's Kirkby plant includes advanced environmental protection and safety features of the type that have become commonplace among modern custom producers. The production area is completely isolated from the sewer, and all effluents and washings from processes are placed in drums and shipped to an approved disposal company. This lets the company use heavy metals such as mercury, chromium, and manganese with the assurance that residues will be disposed of responsibly. Off-gases from vessels and plant air at Kirkby are scrubbed before emission from the building.

Among Lancaster's chemistry strengths are butyllithium reactions, alkali metal reductions, Grignard reactions in tetrahydrofuran, and brominations, alone

or in conjunction with hydrogen peroxide, phosphorus trichloride, triphenylphosphine, or mercuric oxide (Hunsdiecker reaction). Process strengths include sublimation, molecular distillation of unstable compounds, and reactions carried out at –10 °C.

Hardwicke of Elgin, S.C., is an additional beneficiary of BTP's financial strength, according to marketing manager Joseph G. Mancini Jr. Hardwicke's principal expertise lies in continuous brominations, Friedel-Crafts reactions with aluminum chloride on a large scale, Grignard reactions, and a variation on the Ullmann reaction, in which acetal-protected aromatic bromoaldehydes are coupled with potassium phenoxides to form diaryl ether derivatives. Hardwicke has arrangements with other firms to purchase its hydrogen bromide and aluminum salt by-products.

And the former MTM fine chemicals business and plant in Columbus, Ohio, is thriving under ISP ownership. Paul D. Taylor, who is general manager of ISP Fine Chemicals, says the parent has made new investment available to ensure continued compliance with state, federal, and Food & Drug Administration regulations.

Among new purchases for the Columbus facility are improved process controls and analytical instrumentation. Also available is support from the parent research, process engineering, and analytical laboratories in Wayne, N.J. (Taylor came to his new post from heading process engineering in Wayne.) It is also helpful to the new custom synthesis side of the business that ISP is already known to the drug industry as a maker of excipients (formulating additives).

At the newly independent Eastman Chemical, operations including custom production are centered in Kingsport, Tenn., and Batesville, Ark. The new company is no longer linked to Sterling Organics or to the laboratory chemical business as it was under Kodak.

Kodak sold the laboratory chemical business to Fisher Scientific. Fisher has also bought the laboratory chemical company Janssen Chimica, Beerse, Belgium. Janssen Chimica was part of Janssen Pharmaceutica, which in turn is a subsidiary of Johnson & Johnson of the U.S.

Dollar sales are about 20% smaller at Eastman than when Eastman was under Kodak, but production capacity is

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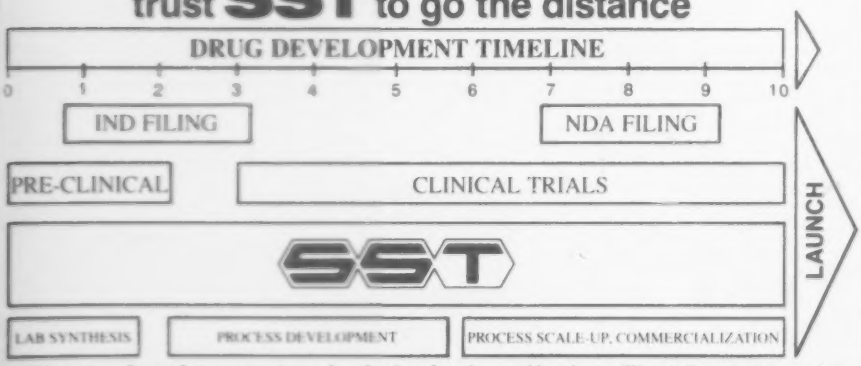

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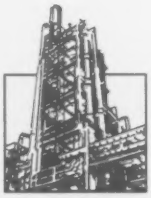

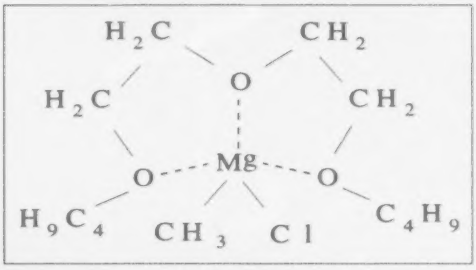

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$(n\text{-}C_4H_9)_4P(CH_3CO_2)\text{-}(CH_3CO_2H)$	Tetrabutylphosphonium Acetate, Monoacetic Acid	17786-43-5
$(n\text{-}C_8H_{17})_4PBr$	Tetraoctylphosphonium Bromide	23906-97-0
$(HOCH_2)_4PCl$	Tetrakis (hydroxymethyl)-phosphonium Chloride	124-64-1

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CIRCLE **7** ON READER SERVICE CARD

Survey identifies causes of chemical plant accidents

Process	% of incidents[a]
Polymerization	48%
Nitration	11
Sulfonation	10
Hydrolysis	7
Salt formation	6
Halogenation	6
Friedel-Crafts	4
Amination	3
Diazotization	3
Oxidation	2
Esterification	1

a Accidents surveyed 1962–87; percents do not add up to 100% because of rounding. **Source:** *Chem. Eng. Res. Des.*, **67**, 361 (1989)

about the same. R. L. (Bob) Morrow, who is vice president and general manager for fine chemicals, says the company will be at a short-term disadvantage owing to the loss of its tie with the laboratory chemicals production plant in Rochester, N.Y. That facility has equipment ranging from 22-L glass flasks to 500-gal reactors for production of small amounts. Morrow says plans are under way to install similar capacity at Eastman. However, he says, Eastman learned a great deal about the custom marketplace and client relations during the relationship with Sterling Organics and the reagent business. Eastman intends to apply those lessons as it ventures out on its own.

At Zeeland, the inclusion under the Cambrex umbrella has meant that Zeeland can take advantage of raw materials, farming out production steps, and technical advice from the other subsidiaries. James K. Datson, business development manager, says Zeeland's own strengths are in resolution of racemic mixtures by classical, diastereomeric crystallization, high-pressure synthesis of amines by reaction of other amines with aldehydes or ketones (reductive alkylation), and production of quaternary ammonium compounds.

Zeeland also can send ammoxidations (reactions with ammonia to make nitriles) to sister company Nepera in Harriman, N.Y. Zeeland has a cost advantage in buying pyridine derivatives from Nepera to use to make advanced intermediates for drugs against the human immunodeficiency virus (HIV). And Zeeland can call on sister

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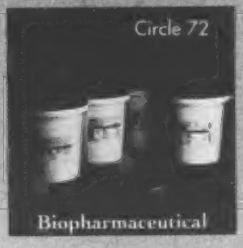

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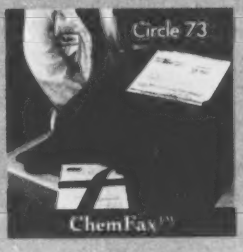

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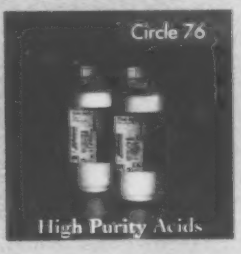

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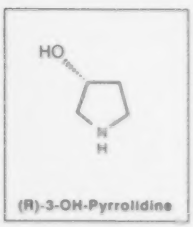

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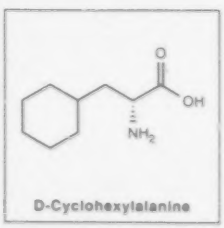

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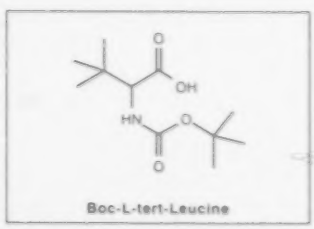

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companies for technical consultation when developing new processes at Zeeland.

The first client for the plant that Sandoz Agro sold to Catalytica will be Sandoz itself. Sandoz had been making ethyl and propargyl esters of 3,7,11-trimethyl-2*E*,4*E*-docosadienoic acid and the isopropyl ester of the 11-methoxy-acid in this plant as insect growth regulators and the housefly attractant 9*E*-tricosene. Catalytica will make these for Sandoz.

But Catalytica's big custom production thrust in East Palo Alto will be toward the drug industry. Catalytica managers say drug companies will be attracted by the firm's expertise in chemical process development generally and by its track record in catalytic processes for pollution abatement and cleaner catalytic production of known, useful intermediates.

For example, Catalytica has developed processes for oxidation of ethylene to acetaldehyde without chlorine cocatalysts; of 2,6-diisopropylnaphthalene to 2,6-dihydroxynaphthalene, 2,6-naphthalenedicarboxylic acid, and 6-hydroxy-2-naphthoic acid with zeolite catalysts; of *m*-diisopropylbenzene to resorcinol; of phenol to catechol; and of spent hydrogen bromide to recovered bromine with oxygen as the sole oxidant.

Sepracor will use the Pharmaglobe plant in Nova Scotia to produce enantiomeric drugs for itself and to place special orders for others. The company has licensed both the asymmetric hydroxylation of olefins invented by organic chemistry professor K. Barry Sharpless of Scripps Research Institute and the asymmetric epoxidation of olefins invented by organic chemistry professor Eric N. Jacobsen of Harvard University. Previously, Sepracor had to contract such reactions from companies in Japan.

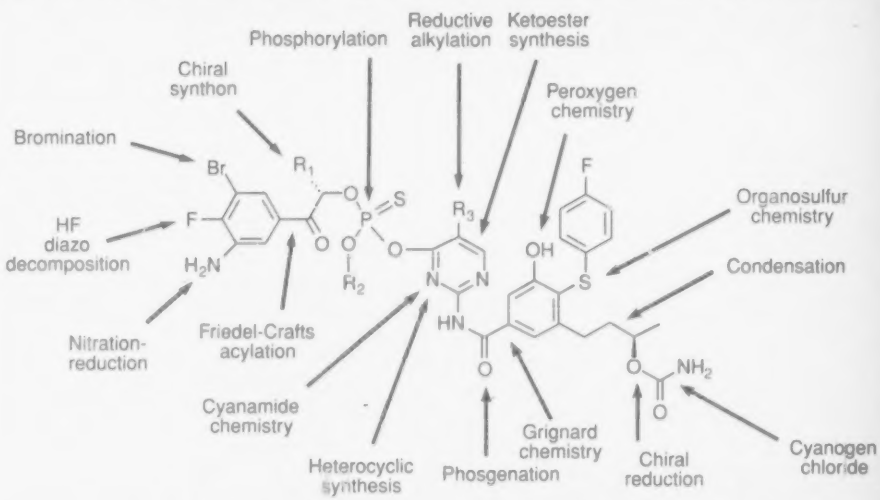
In another thrust in chiral drugs, Sepracor has studied enantiomers of other companies' racemic drugs, discovered unexpected new activities in them, patented the enantiomers, and offered licenses to drug companies generally. The Pharmaglobe plant will serve to produce these in case licensees contract their custom synthesis back to Sepracor.

Both Catalytica and Sepracor began as chemical technology companies. The idea was that they would discover new

products and technologies, patent them, and license the patents. But the thinking in such technology companies has changed as a result of the realization that customers want products rather than technologies. Thus Catalytica and Sepracor are examples of companies that have "backed into" custom chemical production.

The organosilanes and silicones business and plant that UCT bought from Hüls America is the one-time independent Petrarch Systems. UCT has relocated and consolidated its operations at the Petrarch site in Bristol, Pa. John MacMillan, director of technical sales and service at UCT, says UCT will use the Petrarch name for the recognition that it carries. Typical requests for custom production include experimental aerospace resins to resist damage during atmospheric reentry of space vehicles, high-refractive index materials for fiber optics, and monomolecular compounds for academic research.

Molecules of bulk active ingredients become increasingly complex



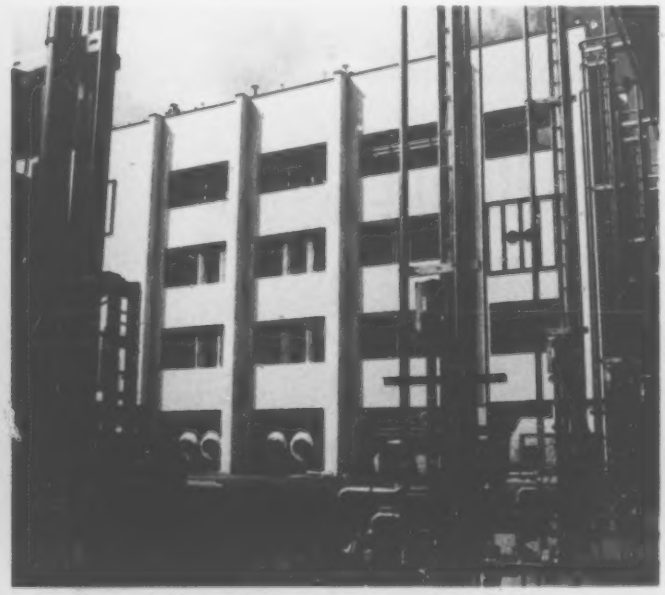
Though totally imaginary, this fanciful structure has often been invoked to symbolize the complexity of new products and the array of techniques brought to bear in their custom production.

Source: Ian Schott, Lonza

The British are coming

The "North America Now" campaign, in which the British custom fine chemicals industry has targeted Canada, the U.S., and Mexico, has just finished its first phase. Representatives of the 10 companies that have assembled under the loosely organized umbrella name UK Fine Chemicals wound up an 11-day tour of the northeastern U.S. in October. They stopped in nine places and gave presentations to a total of 200 people whom they had invited from 32 drug and other specialty chemical companies. Presentations described the collective expertise of the 10 firms. Presentations were followed by mini-trade shows, in which the British companies spread their literature on widely separated tables and invited frank individual discussions about synthetic chemical needs.

The 10 firms that make up UK Fine Chemicals are Boots Chemicals, Nottingham; Contract Chemicals, Prescot, Merseyside; Courtaulds Chemicals, Spondon, Derby; Exchem Industries, Harwich, Essex; Fine Organics (part of Laporte), Middlesbrough, Cleveland; Hickson Fine Chemicals, Castleford, West Yorkshire; A. H. Marks, Wyke, Bradford; Peboc (part of Solvay), Anglesey, Gwynedd, Wales; Robinson Brothers, West Bromwich, West Midlands;



Chemie Linz uses dedicated building (left) for custom ozonolysis, generating ozone from an array of electric spark cells.

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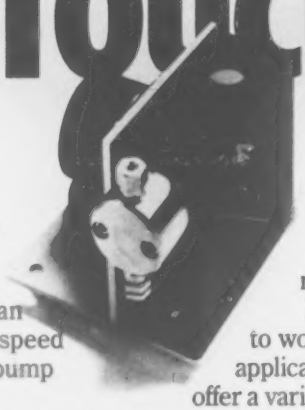

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and Zeneca Fine Chemicals (formerly part of ICI), Blackley, Manchester.

The chemistries emphasized by the 10 firms are amine synthesis, catalytic hydrogenation, chiral synthesis, chloromethylation, cyanation, fluoroaromatic chemistry, Friedel-Crafts reactions, heterocyclic chemistry, nitration, organophosphorus and organosulfur chemistry, peptide synthesis, peroxygen chemistry, and phosgenation. At the final presentations of the tour, Tony W. Bastock, marketing director at Contract Chemicals, singled out British expertise in chiral synthesis and phosgenation for discussion.

Boots Chemicals, Peboc, and Zeneca Fine Chemicals do chiral syntheses. Phosgenations are carried out by Fine Organics, Hickson, and Peboc. Bastock says this illustrates that UK Fine Chemicals is a loose association of mutual competitors and not a cartel. Thus, U.S. companies usually have a choice of British suppliers for the same type of chemistry.

As an example of UK Fine Chemicals' capabilities in chiral chemistry, Bastock cites Boots as a leading producer of (*S*)-ibuprofen. Boots had earlier pioneered in ibuprofen discovery. And Zeneca produces 1,500 metric tons per year of (*S*)-α-chloropropionic acid, an important drug and pesticide intermediate, by enzymatic resolution.

For phosgenation, Bastock says the three purveyors of that service have phosgene generators from the chemical engineering firm of Buss in Pratteln, Switzerland. These generators, located in buildings reserved only for them, are infinitely variable in production rates between a few tens of kilos per hour to several hundred kilos per hour as needed. Thus phosgene is made and used as required, making it unnecessary to buy, make, ship, or store large amounts.

Phosgene is a valuable agent for conversions of acids to acid chlorides, amides to nitriles, primary amines to isocyanates, and alcohols to chloroformates. But its infamy as a war gas has made its responsible use a matter of public concern. The more tractable diphosgene (trichloromethyl chloroformate, $Cl\text{-}CO_2\text{-}CCl_3$) can be used by the three firms as a phosgene substitute in small-scale reactions.

The next phase in the North America Now campaign will be invitations from the 10 British firms to North

American conferees at ChemSpec Europe '94, April 18–21 in Manchester, England, to visit their plants during the trip. Next, the 10 companies will return to the U.S. to exhibit at Chemical Specialities USA '94, Oct. 17–20 in Chicago.

In addition to the British effort, companies have sprung up to market custom chemicals in the U.S. that are to be produced in Eastern Europe. For example, Syntest, a Russian joint stock company in Chernogolovka, near Moscow, offers synthetic services of chemists at 300 academic research institutes in the former Soviet republics. The company also has a U.S. subsidiary, Syntest Princeton, in Princeton, N.J.

In addition, ChemBridge, headquartered in Northbrook, Ill., with offices in Moscow, represents private and state-owned laboratories, pilot plants, and full-scale chemical plants, many formerly military, in the former Soviet republics. And Chemapol USA of Englewood Cliffs, N.J., represents laboratories and plants in both the Czech and Slovak republics.

Marlene Molloy, secretary-treasurer of Syntest Princeton, says the company was formed to earn money to support chemical research at the participating institutes. The institutes can make compounds in amounts from milligrams to kilograms, Molloy says, but are not equipped for commercial-scale production.

Some clients come to Syntest because they want analogs of biologically active compounds that institute chemists have already made. Or clients want an improved or proprietary process to make one of their own compounds.

Molloy cites the example of a U.S. diagnostics firm that wanted a patentable dye invented for a blood test kit. Molloy sent the assignment into the network of institutes and got four responses. One respondent laboratory fulfilled the task so well that the diagnostics firm asked to have the chemist sent to the U.S. to work on site for a few months.

On another occasion, a U.S. agricultural chemical company screened a battery of related compounds for a desired activity, then asked to have a certain analog made that was not in the original lot. The project eventually grew to requests for many analogs. The agrochem company explained to Molloy that making the compounds themselves would have cost a lot more.

According to Pavel Janacek, presi-

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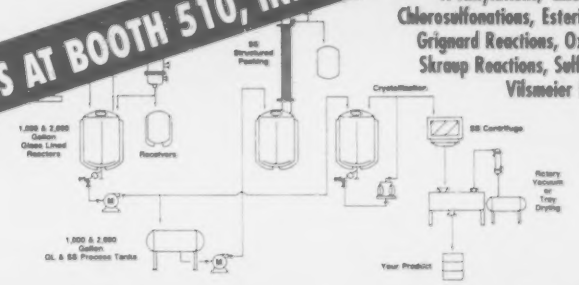

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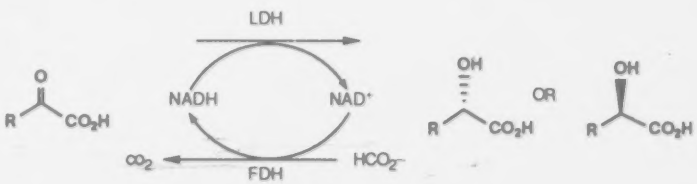

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dent of Chemapol USA, "Chemical and pharmaceutical manufacture is one of the most advanced areas of industry in the Czech and Slovak republics. The stable situation in both countries, low labor costs, a traditionally skilled work force, and a solid R&D base have given Chemapol USA a promising start in the U.S. market."

Janacek says that ailing economies have led to underuse of chemical and drug production capacity in both republics. U.S. clients thus have opportunities to buy custom production by skilled chemists and technicians. Some of the plants are FDA-approved, and others are seeking approval.

Locating a producer

The reconfiguration of the custom chemical producing industry has added to the already inherent difficulties of finding a contract producer, developing a process, and setting a price for a compound that essentially does not exist. That there are a few hundred firms in the U.S. alone promoting their custom services is not much help. Companies looking for custom chemical production can use conventions, directories, and agents to find sources.

Some sources tell C&EN that sessions of the Division of Small Chemical Businesses at national meetings of the American Chemical Society can be useful occasions to make contacts. Perhaps the most important meetings are those called Informex, put on annually by the Synthetic Organic Chemical

Fine chemicals have special characteristics

Characteristic	Industry segment: Commodity chemicals	Fine chemicals[a]	Specialty chemicals
Product life cycle	Long (> 30 years)	Moderate	Short (< 10 years)
Product slate	Narrow	Very broad	Very broad
Product volumes	>> 10,000 tons per year	< 10,000 tons per year	Variable
Product price	< $5.00 per kg	> $10 per kg	Variable
Product differentiation	Nonexistent	Low	Very high
Service differentiation	Low	Average	High
Value added	Small	High	Moderate/high
R&D focus	Process improvement	Process development	Product development
Capital intensity	Low	Moderate	High
Customer	Not a chemist	Chemist	Not a chemist

a. Fine chemicals is the industry segment that is most often concerned with custom synthesis. **Source:** Arthur D. Little

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Manufacturers Association (SOCMA). Informex is the only exposition devoted solely to interests of custom chemical production.

Industry observers tell C&EN that both exhibitors and attendees are "high quality" with respect to fruitfulness of contacts during visits to booths. This is said to be because SOCMA charges fees not only to exhibitors but also to attendees. SOCMA member firms will pay $1,000 per booth and nonmembers $3,500 at the 1994 Informex. Attendees from member firms will pay $250 each and from nonmember firms $350.

Between Informex meetings, there are directories. Ann Hart of Brandon Associates, Merrimack, N.H., which publishes such directories, has a few tips for those making their way through directories and their cross-indexes.

For someone seeking hydrogenation of a nitrile to an amine, she advises, "Pay particular attention to the pressure required for the hydrogenation. Many firms offer low-pressure capabilities, which are not suitable if your compound requires 1,000 psi or greater."

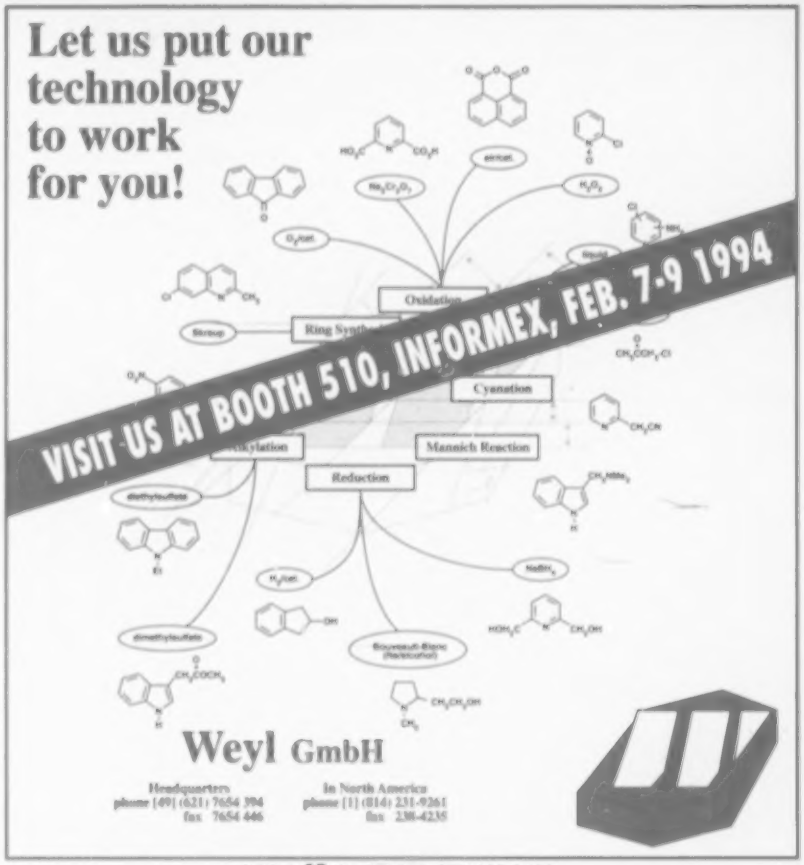
Further, using hydrogenation as an example, "Next, look over their equipment listing for an estimation of the general sizes of their production equipment," Hart says. "Clearly, if you need a million pounds a year, a firm with a 50-gal autoclave won't do.

"If your project requires a special chemical, perhaps one that requires special handling, consult the 'Special Raw Materials' and 'Handle Toxics'? entries of those firms you have identified so far. Consider locale, too, if you believe having a custom producer near you is worthwhile."

In addition to Informex and directories, there are two types of agents one can use. One type represents no particular supplier of custom production and relies on personal contacts to bring a client and suitable supplier together to mediate an agreement. Examples are Richman Chemical, Ambler, Pa., and Sithean Corp., Richmond, Va.

The second type of intermediary represents specific custom producers and becomes an actual part of the project, taking possession of the custom-produced goods and reselling them to the client. Examples are Davos Chemical Corp., Englewood Cliffs, N.J., and Interchem Corp., Paramus, N.J.

Paul Harris, vice president for commercial development at Sithean, says



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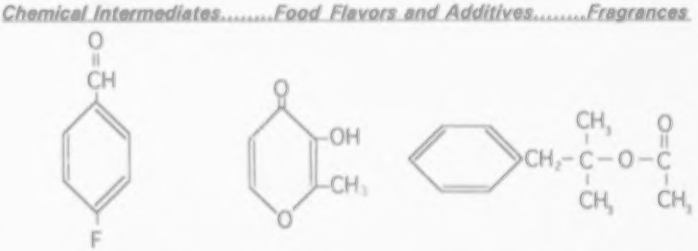

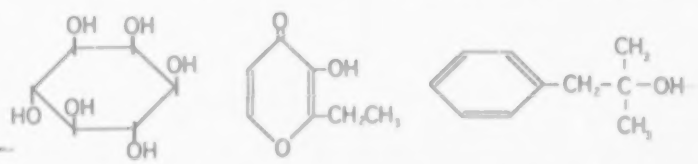

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CIRCLE 41 ON READER SERVICE CARD

Conventions unite contract chemical manufacturers and customers

Three annual conventions have become established in the U.S. to bring together sellers and prospective buyers of custom chemical production. The 9th Annual Informex Trade Show & Technical Symposium will be held this week, Feb. 1–3, in New Orleans. Also, Chemical Specialities USA '94 will meet in Chicago, Oct. 18–20, for its fifth year. And although enantiomers of chiral compounds are only a subset of fine chemicals, Chiral USA '94 to be held in Reston, Va., May 5–6, will be the second U.S. meeting of an annual symposium dealing with producing chiral compounds.

Informex is put on by the Synthetic Organic Chemical Manufacturers Association (SOCMA) and is the only convention devoted solely to custom chemical production. This year's meeting features a technical session and three-day exposition and is expected to draw almost 200 exhibitor firms and 1,000 attendees. The technical session is a panel discussion, "Selecting a Toll Manufacturing Site—The New Criteria."

Next year's Informex will be in Nashville, Feb. 20–22, 1995. For information, contact SOCMA, 1330 Connecticut Ave., N.W., Washington, D.C. 20036; phone (202) 659-0060.

Both Chiral USA '94 and Chemical Specialities USA '94 are organized by Spring Innovations, Stockport, England. For information about either event, in North America contact Brandon Associates, P.O. Box 1244, Merrimack, N.H. 03054; phone (603) 424-2035. Chiral USA '94 consists of 21 papers given over one and a half days on topics including business prospects and government regulation of chiral drugs and pesticides as well as enantioselective reactions and catalysts, biotransformations, resolutions, and auxiliary reagents.

Chemical Specialities USA '94 includes technical sessions over one and a half days as well as a two-day exposition organized by FMJ International Publications, Redhill, England. Industrial chemists, academicians, and consultants will speak at symposium sessions. More than 100 exhibitor firms will be in the exposition, most of whom offer custom production.

most people who come to him have had the function of buying custom chemical production for their companies for only a short time. It may be their first or second such project. These people find Sithean in a directory, or another firm for which Sithean has worked recommends them. Sithean works on commission, which is only paid if the project is completed.

"So you have to get the project at the right place," Harris says. "You have to have a good transfer of information back and forth—sometimes people forget to say something. It's like a marriage. You can't hide things from one another. Also you have to get the project priced right." Harris emphasizes that there is no market that acts to set the price of a project.

Edward Richman, president of Richman Chemical, has also acted as a mediator to bring a customer and a manufacturer together for a commission. But for the most part, Richman Chemical acts as a project manager. As such, Richman subcontracts the project to a manufacturer, bills the customer, and remits to the manufacturer.

This means that Richman is the firm responsible for the project—overseeing it and meeting any problems. This helps in case problems arise and uncertainty exists over whether a purchasing agent, research director, or someone on the business side should handle it.

Project management also helps if the customer and manufacturer have different modes of doing business. For example, the customer may want a price per kilo, but the manufacturer charges per hour of equipment use. Richman can also buy the starting material, relieving the customer company of risk of liability for operations on material it owns. In addition, Richman relates the time dependence of the customer's need for the chemical. Then the company can be sure that the manufacturer will have sufficient lead time to meet the customer's need.

Robert G. Golle, business development manager at Interchem, says his firm represents mostly custom producers overseas, although Interchem does work for Poly Organix of Newburyport, Mass., and Riverside Organics of Detroit. Most of these companies are

registered according to good manufacturing practices (GMP) with FDA, or under some form of ISO 9000. Interchem places a project with one of its clients, arranges to bring the compound through customs to the U.S., and handles such paperwork as certificates of analysis and safety data sheets. Golle says staying within Interchem's group of clients helps ensure maintenance of confidentiality.

Dealing from strengths

Once a custom producer has been selected, the client will find that there has been a change from previous modes of doing business. As William T. Scott, sales vice president at ChemDesign Corp., Fitchburg, Mass., puts it, "The 'one-man' operation of the past has been replaced by a group of skilled professionals knowledgeable in the many disciplines that are necessary to run a successful custom chemical operation."

ChemDesign's Fitchburg plant is an example of how custom chemical production must be done today. For one thing, the plant is sited in a scenic wooded area of a populous state. Indeed, the stand of trees is adjacent to and a continuation of the Leominster State Forest, an unforgiving environment.

As part of environmental protection, ChemDesign has installed a liquid nitrogen chiller that receives offgases through ducts from all reactors and vessels in two buildings. All gases are

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CIRCLE **12** ON READER SERVICE CARD

Azo Polymerization Initiators

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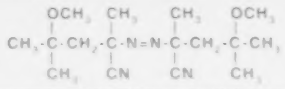
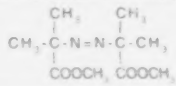
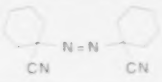
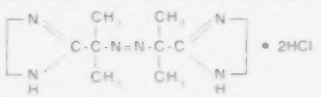
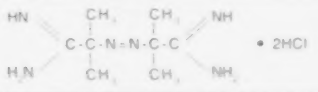
V-70  $t_{1/2}$=33°C

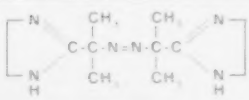
V-601  $t_{1/2}$=66°C

V-40  $t_{1/2}$=88°C

Water Soluble

VA-044  $t_{1/2}$=44°C

V-50  $t_{1/2}$=56°C

VA-061  $t_{1/2}$=61°C

$t_{1/2}$ = 10 hour half-life decomposition temperature

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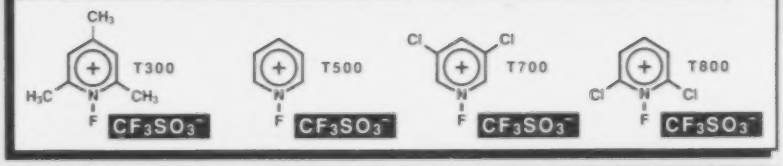
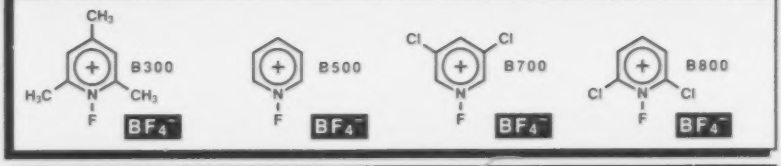


FP-B SERIES



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chilled to -120 °F, which condenses out even such volatile and toxic compounds as methylene chloride. Columns of activated charcoal serve as a "polishing" step afterward.

Condensate from the chiller, together with those waste solvents that are not recycled, goes to companies with permits either to blend them with fuel oil or incinerate them. Airco supplied the original equipment, which was modified by ChemDesign engineers, and today Airco is supplying units based on cooperatively improved designs.

Once any organic compounds are separated from process water, that water goes to a purification plant. This plant separates inorganic salts as a sludge and sends purified water to boilers and cooling towers. Because such units function by boiling and evaporating water, little process water is discharged from the site.

One of ChemDesign's strong suits is high-purity compounds, according to George V. Austin II, who is senior vice president. One type of compound made to special order is diazonaphthoquinones. These are additives to microlithographic photoresists for fabrication of integrated circuits on silicon wafers. Purity requirements are greater for these than for any drug intermediate. In particular, metal contamination must be kept below 100 ppb.

Another recently added strength is a hydrogenation reactor from Buss, the Swiss chemical engineering firm. Such reactors cost $1 million to buy and another $1 million to install, Austin says. But their recirculating loop design ensures especially safe operation, which should give peace of mind to customers as well as to ChemDesign.

But there are limits on what ChemDesign will accept. The company doesn't do phosgenations and air or nitric acid oxidations. Also ruled out is use of such known carcinogens as benzene, and suspected carcinogens are considered carefully. At the end of exhaustive analysis, the company submits a proposal many dozens of pages long to the prospective customer. Each proposal must be signed off by board chairman Richard E. T. Brooks.

Chemie Linz North America also deals from strength, says Nitin Parekh, who is director of new business and technology. The parent company, Chemie Linz of Linz, Austria, is one of the few firms that offer large-scale cus-

tom ozonolysis. Other strengths are nitric acid oxidations to carboxylic acids, biocatalytic syntheses and resolutions of alcohols, carboxylic acids, and cyanohydrins. The company carries out the Ritter reaction to make custom acrylamide mononers. It also boasts possession of Buss loop hydrogenation and general purpose reactors.

The strength of Quality Chemical, Jackson, Miss., is partly that of its parent, First Chemical Corp., which, in turn, is a subsidiary of First Mississippi Corp. Carl (Bill) Arnold, marketing manager at Quality Chemical, says this relationship yields the company a steady stream of capital for expansion at its two custom plants in Dayton, Ohio, and Tyrone, Pa. Also, some of the people who do the regulatory paperwork for Quality Chemical are actually on the payroll at First Chemical. And Quality's own R&D staff is supplemented by a much larger laboratory and pilot plant of the parent. Arnold says Quality is thus a small company, like many others devoted solely to custom production. But the company can call on much larger resources. And Quality is free to devote itself to custom production without worries about setting aside production capacity for in-house products.

At Ruetgers-Nease Corp., State College, Pa., John C. Wetzel says of custom production, "The whole thing is regulations, permits, safety, the environment, being in full compliance, and going through audits." Wetzel, who is technical marketing manager for organic intermediates, points out that the company had no environment, health, and safety department 10 years ago. Then five years ago, one person was assigned that duty. Today the department has a staff of eight.

Indeed, the company has certain technological requirements of customer prospects who bring their processes or new compounds to State College. As to the chemistry, Ruetgers-Nease would like to be told reaction components and conditions, step conversions and yields, simple kinetics, basic thermochemistry, analytical methods used, and product specifications. Concerning the process, customers should describe operating parameters, equipment needs, materials of equipment construction, characterization of wastes, control limits, mass and energy balances, and experience in the customer's pilot plant. Then the company would like to know of any toxicity, fire, or explosion hazards.

Ruetgers-Nease is set up for fast responses to customer queries, Wetzel says. In just two to four weeks, the companies can sign a secrecy agreement, the client can disclose what technology it has, and Ruetgers-Nease can respond with a preliminary cost estimate.

Safe, economical processes

In keeping with the call by Polastro of A. D. Little for cost-effective processes that are safe and environmentally acceptable, a number of tools have been developed to help custom producers achieve this goal. For example, Guenter Grethe, who is director of scientific applications at the office of Molecular Design in Basel, Switzer-

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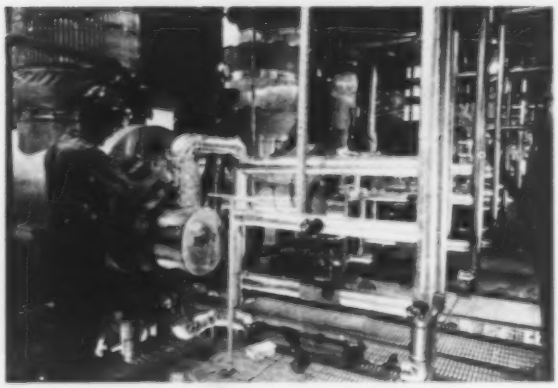

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land, cites uses of his firm's data retrieval programs to seek improved synthetic routes. And chemical engineer Alfred Schnyder of the consulting firm that bears his name in Rieden/Nussbaumen, Switzerland, tells of using reaction calorimetry and differential scanning calorimetry to characterize reactions.

Grethe points to how custom chemical producers can use database computer programs to design improved processes to clients' target compounds, find buyers for excess stocks of intermediates made as parts of previous custom orders, and identify reagents to add to the firm's line of permanent specialties. He cites the example of a series of spirosuccinimides that were found by medicinal chemists at Wyeth-Ayerst Laboratories to inhibit the enzyme aldose reductase. This enzyme reduces glucose to sorbitol, which is thought to accumulate and cause complications of diabetes.

The published syntheses [*J. Med. Chem.*, **35**, 4613 (1992)] each took six steps beginning with substituted *o*-cyanobenzoate esters. These starting materials had to be made by four different routes, depending on the substituents. And one of the six steps liberated hydrogen cyanide.

Grethe has shown how Molecular Design's reaction retrieval systems allow design of a sequence that has only four steps, begins from more easily accessible substituted phthalimides, and eliminates generation of toxic by-products. Reduction of the number of steps alone from six to four makes the method cheaper. But it also reduces the number of wastewater streams to be treated, which further lowers the cost and enhances environmental acceptability.

In addition, one of the four new steps uses trimethylsilyl cyanide. If a producer were to make trimethylsilyl cyanide as a part of custom manufacture of spirosuccinimides, the reagent could be added to the company's catalog for sales to others.

Grethe also gives the example of a producer who may have made some substituted difluorobenzenes as part of an earlier custom order. A search through Molecular Design's Drug Data Report program would turn up two U.S.-approved difluoroquinolone antibacterials plus 16 more under development that use these intermediates. Companies involved in producing these quinolones

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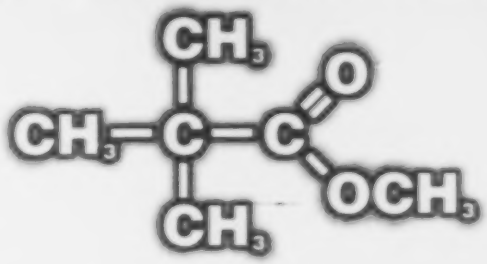

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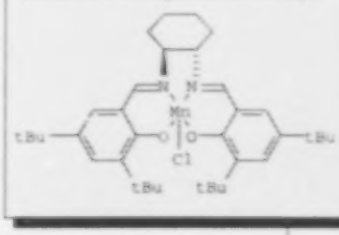

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might be customer prospects for the surplus difluorobenzenes.

After the custom producer or client has made the synthetic sequence as efficient and "user and environmentally friendly" as possible, each step must be examined to determine if it represents a stable process. Engineering consultant Schnyder cites a study of heat-triggered explosions in chemical plants between 1962 and 1987 that pointed to several causes, including insufficient knowledge of process chemistry and thermochemistry, incorrect process management, poorly trained workers, and improperly designed cooling, monitoring, and safety systems.

He analyzes the nature of fine chemicals production to show why heat-triggered explosions are much to be feared in the multipurpose plants used to do custom manufacture. First, the reactions tend to assemble larger molecules from smaller ones. This means that the entropy is decreased. For the free energy of such reactions to be favorable overall, there must be a large enthalpy of reaction. Thus these reactions will generate considerable heat. Indeed, almost half of the thermal explosions in the 1962–87 survey occurred during polymerizations. Schnyder points out that stirring and crystallization are also processes that can generate heat.

Second, Schnyder says, the starting materials of fine chemicals production have a lot of free enthalpy, so they are very reactive. This means that the desired reaction is almost always accompanied by side reactions and such subsequent reactions as decomposition. Decomposition can become autocatalytic (self-sustaining, out-of-control) in reaction mixtures that overheat.

Third, the reaction temperature reported by the research group to the production team is usually based only on the noted influence of reaction temperature on product quality. Researchers may not have considered whether that temperature is commensurate with process stability on a large scale.

Fourth, the batch nature of custom production operations make temperature controllable only by the cooling system. In semibatch work, one reactant is added gradually, and temperature may also be controlled by the rate of dosing.

Fifth, custom producers are usually under pressures of time and efficiency of equipment use. This means that they will strive for the most concentrated reaction mixtures. But concentrated reaction mixtures are the ones most likely to alter greatly in thermal characteristics as the reaction proceeds.

A reaction could run away if done under conditions where it is inherently unstable. For example, Schnyder points out that rate of heat generation increases exponentially with reaction temperature. Thus a graph of heat generation versus temperature curves sharply upward. But rate of heat removal is a

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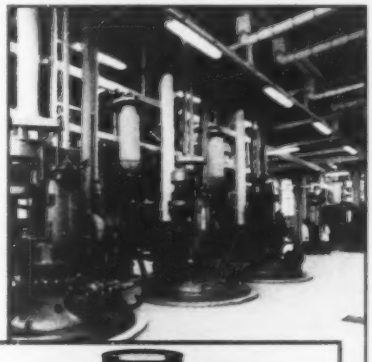

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linear function of temperature difference between reaction mixture and coolant. So a graph of that function is a straight line. The straight line intersects the curved trace at two reaction temperatures, lower and upper, where rate of heat generation equals rate of removal.

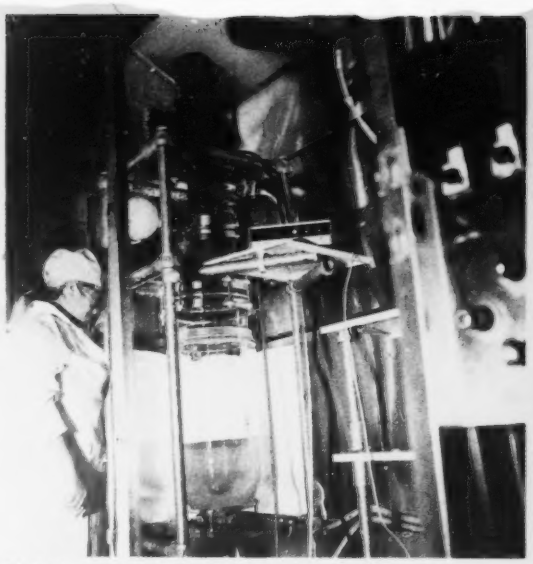
If the reaction is run at the lower temperature, and if a disturbance causes a temperature rise, rate of heat removal will exceed that of generation, and the temperature will subside back to the original value. These are stable conditions. But if the reaction is run at the upper temperature, a temperature increase leads to an excursion, and there is nothing that plant operators can do to regain control.

A crisis could also develop if stirring or coolant flow stops. The question is whether the reaction continues, heat builds up, and a decomposition reaction sets in; or whether the reaction stops because operators stop adding reactant.

Schnyder recommends designing the process to be as close to dose-controlled as possible. The reaction rate should be faster than the dosing rate so that the added reactant is consumed at once. Then in case of emergency, no excess reactant would continue to contribute to heat buildup.

Ironically, operating at too low a temperature also can lead to a runaway reaction. This is because reaction rate increases or decreases with temperature. At too low a temperature, the reaction is too slow, and dosed reactant may accumulate. Schnyder advocates use of reaction calorimetry and differential scanning calorimetry to characterize processes intended for scaleup.

Schnyder's firm provides such analyses for companies too small to do them themselves. The need for such information is recognized. For example, Ruetgers-Nease lists "simple kinetics" and "basic thermochemistry" among points of information required of clients when clients' own technology is to be used. □



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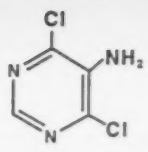

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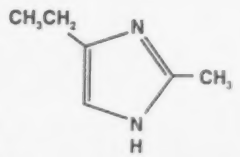
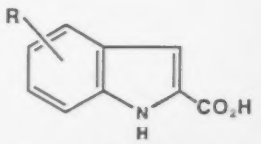


2-Methyl-4-Ethyl-Imidazole



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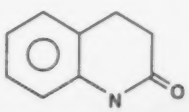

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